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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,201	CROW, MARY K.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4/25/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment(2 pages)* .

DETAILED ACTION

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of a U.S. provisional Application 60/256,673 filed December 19, 2000, is granted.

Specification

Tables 1-5 are submitted as unnumbered pages. As the tables are included in the specification, they too require page numbers. Appropriate correction is required.

Election/Restrictions

Applicant's election with traverse of Group I(claims 1-3) and further, the non-species election of the invention of claims 1-3 drawn specifically to systemic lupus erythematosus, in the Paper filed 5/2/2003 is acknowledged. Applicant's arguments filed 05/2/03 have been fully considered but they are not persuasive. The traversal is on the ground(s) that the office has mischaracterized the relationship between the methods of Groups I-VI as even though they are patentably distinct inventions, they are not required to be restricted unless one of the following reasons appear (MPEP 808.02): Separate classification, Separate status in the art; or Different field of search. The examiner maintains that each group is characterized by a method with either a different function or one that utilizes different method steps and reagents. Furthermore each of the different diseases listed in claim 3 include inherently different characteristic and distinct biomolecules(specific to the disease and further to the actual type of biomolecule), nucleic acid, protein, antibody etc, each being distinct as their composition is drastically different, ie nucleic

acids are composed of nucleotides joined by phosphodiester linkages, while proteins and antibodies are composed of sequential amino acids joined by peptide bonds. In this way, all conditions of MPEP 808.02(Separate classification, Separate status in the art; or Different field of search) are realized by the six different inventions in this application. In response to applicant's arguments concerning group I and II specifically, a method for identifying a gene associated with a disease(Group I) and a method for identifying an individual at risk or suffering from a complex disease(Group II), require different fields of search as different method steps are involved, such as group II's provision of a sample from an individual. Thus, the search and examination of groups I and II for example would be undue burden as the limitations encompassed by each groups claims are different and the search would not be coextensive. Furthermore, applicant should further note that their "species election" was improper as no species requirement was made, only a restriction requirement including an election of a single disease for which to examine the elected method. Applicant should note that the method with respect to each disease represents patentably distinct subject matter as each disease is quite different and inherently encompasses distinct, characteristic biomolecules. Examiner reaffirms that the groups are properly separated as their inclusive methods are comprised by different method steps in order to accommodate the different biomolecules that are characteristic to each method and the elected disease. The examiner maintains the restriction requirement made previously, as each group is correctly separated and therefore make the restriction requirement final.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Kimberland et al.(Human Molecular Genetics, 1999, Vol. 8, No.8, 1557-1560).

Kimberland et al. teach a method of identifying the Beta-globin and retinitis pigmentosa-2(RP2) genes involved in a complex disease comprising the steps of:

(i) identifying a region of the genome neighboring a disease-associated marker for Beta-thalassemia and X-linked retinitis pigmentosa(Pg. 1557);

(ii) comparing the sequence of the 5' regulatory region of a consensus L1 sequence to the intronic region of genes or predicted genes or to the 5' or 3' regulatory of genes or predicted genes(Pg. 1558, Figure 1 comparison); and

(iii) identifying the Beta-globin and retinitis pigmentosa-2(RP2) genes containing a full-length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region, wherein said genes identified in step (iii) are involved in the complex diseases Beta-thalassemia and X-linked retinitis pigmentosa(Pgs. 1557-1558).

The reference further teaches the accession numbers AF148856 and AF149422(See attached sequence alignment of SEQ ID NO:1 and U09116) that correspond respectively to the L1 elements present in the intronic sections of the retinitis pigmentosa-2(RP2) and Beta-globin genes respectively. In addition, Kimberland et al. teach that to date, 12 L1 retrotranspositions

into genes have been reported as disease-causing mutations. Kimberland et al. teach the generation of their consensus sequence by comparing the sequences of seven full-length elements(L1.2A, LRE2.1, L1.3, L1.4, L1.19, L1.20 and L1.39)(Figure 1) to which the L1 sequences of the retinitis pigmentosa-2(RP2) and Beta-globin genes share 99.4% and 99.9% identity respectively(Pg. 1557).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a gene involved in Beta-thalassemia and X-linked retinitis pigmentosa, comprising the steps of:

(i) identifying a region of the genome neighboring a disease-associated marker for Beta-thalassemia and X-linked retinitis pigmentosa;

(ii) comparing the sequence of the 5' regulatory region of a consensus L1 sequence to the intronic region of genes or predicted genes or to the 5' or 3' regulatory of genes or predicted genes; and

(iii) identifying the Beta-globin and retinitis pigmentosa-2(RP2) genes containing a full-length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region, wherein said genes identified in step (iii) are involved in the complex diseases Beta-thalassemia and X-linked

retinitis pigmentosa, does not reasonably provide enablement for the method of identifying any gene involved in any complex disease by identifying any region of the genome neighboring any disease-associated marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In addition, Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-3 are broadly drawn to a method of identifying any gene involved in any complex disease by identifying any region of the genome neighboring any disease-associated marker, said method comprising identifying all genes containing a full length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region, wherein all of these genes containing L1 elements as prescribed above are involved in a complex disease. The specification teaches that LINEs(L1 elements) are believed to be fragments of a nucleotide sequence that has been distributed at many locations throughout the genome, and contain a 5' regulatory region and two open reading frames(ORF) that can encode two proteins (ORF1 and ORF2). These two ORFs

are transcribed into mRNA, which are copied back (or parts of it) into DNA, and the DNA inserted back into the genome. Thus the specification teaches the key role of LINEs in driving the increasing sophistication and diversity of the immune system throughout evolution to be supported by the heavy load of those elements in the segments of the genome encoding the MHC, immunoglobulin heavy and light chains, and T cell receptors. The specification also teaches that the presence of an L1 element within the regulatory region or in an intron of a gene can modify the expression of that gene and if that gene product is important in the immune or inflammatory pathways, altered expression of the gene product can contribute to autoimmune disease(Pg. 36). The specification teaches in Table 1 the chromosomal location of proposed SLE disease loci and full-length high fidelity L1 elements with the percent sequence identity being determined in comparison to nt 1-884 of accession no. U09116, a consensus sequence. The specification on page 11 also teaches that a "susceptibility locus" for a particular disease is a sequence or gene locus implicated in the initiation or progression of the disease. The specification additionally teaches that among the first and best studied germline insertions are those into factor VIII and dystrophin genes of individuals with sporadic hemophilia and muscular dystrophy. However, the specification has not established a clear correlation between any gene containing a full length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region and all complex diseases. Although a few examples are referenced, no teaching of similarities or commonalities of a shared characteristic between the L1 elements capable of conferring complex disease exists. Furthermore the specification is silent to teachings of known markers of complex diseases. The specification omits any teachings in Table 1 of the

"proposed" associations of the markers as SLE disease loci. There are no teachings in the specification regarding specific markers that have been associated with complex diseases. The specification does not teach the identification of any and all genes containing a L1 element as stated above that are necessarily associated with any and all complex diseases.

As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one can only readily anticipate a method of identifying a gene involved in Beta-thalassemia and X-linked retinitis pigmentosa, comprising the steps of:

(i) identifying a region of the genome neighboring a disease-associated marker for Beta-thalassemia and X-linked retinitis pigmentosa;

(ii) comparing the sequence of the 5' regulatory region of a consensus L1 sequence to the intronic region of genes or predicted genes or to the 5' or 3' regulatory of genes or predicted genes; and

(iii) identifying the Beta-globin and retinitis pigmentosa-2(RP2) genes containing a full-length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region, wherein said genes identified in step (iii) are involved in the complex diseases Beta-thalassemia and X-linked retinitis pigmentosa. The art teaches the method above and has enabled claims 1 and 2 only with respect to the diseases Beta-thalassemia and X-linked retinitis pigmentosa. The art has taught a known correlation between the insertion of the L1 elements sharing at least about 95% similarity to the sequence of nucleotides 1-884 of SEQ ID NO:1 and the Beta-globin and retinitis pigmentosa-2(RP2) genes and further the causative relationship that exits between this transposition and disease onset. In contrast, one cannot readily anticipate a method of identifying any gene involved in any complex disease by identifying any region of the genome neighboring any disease-associated marker, said method comprising identifying all genes containing a full length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region, wherein all of these genes containing L1 elements as prescribed above are involved in a complex disease from the art. More simply, one cannot anticipate that every gene containing a L1 element will be involved in a complex disease. In the absence of specific guidance as to how to identify other markers associated with complex diseases and furthermore their response to a L1 insertion it would require undue experimentation to identify the additional genes that may be associated with complex diseases. Both the specification and art teach that much unpredictability exits concerning the practice of this broadly claimed method. The specification uses the results obtained with a small amount of independent, unrelated gene markers(Page 29 of

Specification) and extrapolates them to all genes and all complex diseases. Also the unpredictability in the state of the art is emphasized by the teachings in the Applicant's specification regarding the fact that "as the sequencing of the human genome is still in progress, precise locations and DNA sequences of genes and disease loci remain subject to revision pending completion of the full genome analysis in multiple individuals". Which is to say that the existence of known, associated genetic markers is currently unpredictable. The post-filing date art corroborates the unpredictability in the specification by teaching that much uncertainty exists in the potential for L1 integrations alone not even considering a correlation to specific complex diseases. Gilbert et al. teach that "little is known about how L1 integration is completed"(Cell, Vol. 110, 315-325, 2002). The reference points to further unpredictability in this claimed method through their teaching of "an unexpected outcome of our study ids that L1 retrotranspositions can result in a variety of target site alterations" and even more poignant to this claimed method's unpredictablility the teaching that their "data provides strong experimental support for the hypothesis that L1 EN generates a sequence specific endonucleolytic nick in the bottom strand of the target sequence to initiate L1 retrotransposition"(Cell 322). This teaching concerning the unpredictable outcomes that result from L1 insertions makes the claim of being able to identify any and all genes associated with any all complex diseases to seem prophetic. Another piece of post-filing date art further substantiates the unpredictability present in this method of gene identification. Szak et al. teach that "the precise determination of the boundaries of L1 elements is complicated by the highly variable sequence and anatomy of L1 insertions." "The most variable features of the L1s are the poly(a) tail, which has a variable length and can contain simple repeats…but many changes have also been reported in the coding regions of

young L1s, especially in a segment of ORF1"(Genome Biology, Vol. 3, 2002). With respect to the present invention, one cannot readily anticipate any or all of the genes that may be involved in any or all complex diseases, by solely the identification of an L1 element as prescribed in the claims. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The specification provides no guidance as to how to predictably identify genes with L1 insertions that are reliably correlated with known markers of specific complex diseases. Furthermore, the specification fails to teach the even the known disease markers with which their L1 elements would be correlated. Lastly they was no connection then between a specific (or set of) insertions that were consistently reproducible in their association to a certain known disease marker. The ability to establish this correlation is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. Therefore, neither the specification nor the art provides the guidance necessary to how to predictably identify genes with L1 insertions that are reliably correlated with known markers of specific complex diseases. Thus, in light of the lack of breadth of the claims, the lack of guidance and working examples in the specification, the high level of unpredictability in the prior art and the quantity of experimentation necessary to practice the claimed invention, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with claims 1 and 2 and it would further require undue experimentation to practice the invention set forth in claim 3.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-3 recites the limitation "the sequence of the 5' regulatory region" in line 4. There is insufficient antecedent basis for this limitation in the claim and it is unclear if the sequence is in a region of the genome, in a disease-associated marker, or in a gene involved in a complex disease.

B. Claims 1-3 recites the limitation "the intronic region of genes or predicted genes" in line 5. There is insufficient antecedent basis for this limitation in the claim and it is unclear if the intronic region to which it is referring is in a region of the genome, in a disease-associated marker, or in a gene involved in a complex disease.

C. Claims 1-3 recites the limitation "the 5' or 3' regulatory region of genes or predicted genes" in lines 5 and 6. There is insufficient antecedent basis for this limitation in the claim and it is unclear if the 5' or 3' regulatory region of genes or predicted genes to which it is referring is in a region of the genome, in a disease-associated marker, or in a gene involved in a complex disease.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (703)308-2199. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

7/24/2003

W. Gary Jones
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